Search Strategy

FILE 'USPATFULL' ENTERED AT 11:25:15 ON 29 SEP 2003

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                E GILLES GUICHARD/IN
                E GUICHARD GILLES/IN
L1            3 S E3
                E REGENMORTEL M/IN
                E BRIAND JEAN PAUL/IN
L2           12 S E2 OR E3 OR E4
L3            9 S L2 NOT L1
                E SLYVIANE MULLER/IN
                E MULLER SLYVIANE/IN
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FILE 'MEDLINE' ENTERED AT 11:28:39 ON 29 SEP 2003

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                E GUICHARD G/AU
L4           38 S E3 OR E4
                E REGENMORTEL M/AU
L5            5 S E4 OR E5
L6            5 S L5 NOT L4
                E BRIAND J P/AU
L7          162 S E3 OR E5
L8          128 S L7 NOT L4
                E BENKIRANE N/AU
L9           20 S E3 OR E4
L10           8 S L9 NOT L4
                E FRIEDE M/AU
L11          11 S E3 OR E4
L12           3 S L9 AND ANTIGENICITY
                E BONELLI ?/AU
L13         491 S BONELLI ?/AU
L14          18 S L13 AND PEPTIDE
L15           2 S L14 AND ANALOGUES
                E CHOREV M/AU
L16         136 S E3 OR E4
L17           3 S L16 AND PEPTIDOMIMETICS
L18          12 S L16 AND (RETRO-INVERSO OR RETROINVERSO)
L19        1016 S (IMMUNORETROIDS OR RETROINVERSO OR RETROPEPTIDE? OR RETRO-INV
L20         129 S L19 AND (IMMUNORETROID? OR IMMUNO-RETROID? OR RETRO-INVERSO O
L21         115 S L20 NOT L4
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FILE 'USPATFULL' ENTERED AT 12:11:34 ON 29 SEP 2003

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L22        5254 S (IMMUNORETROID? OR IMMUNO-RETROID? OR RETROINVERSO OR RETRO-I
L23         469 S L22 AND (IMMUNORETROID? OR IMMUNO-RETROID? OR RETROINVERSO? O
L24         339 S L23 AND (ANTIGEN? OR IMMUNOGEN?)
L25          14 S L24 AND (FOOT-AND-MOUTH-DISEASE VIRUS OR FMDV)
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L1 ANSWER 2 OF 3 USPATFULL on STN
2002:246531 Methods for the detection of antibodies associated with autoimmune disorders and infectious agents employing immunoretroid peptides derived from antigens associated with said disorders and agents.
Guichard, Gilles, Strasbourg, FRANCE
Muller, Sylviane, Strasbourg, FRANCE
Briand, Jean-Paul, Strasbourg, FRANCE
Van Regenmortel, Marc, Strasbourg, FRANCE
Biomerieux S.A., Marcy-L'Etoile, FRANCE (non-U.S. corporation)
US **6455244** B1 20020924
WO 9524916 19950921
APPLICATION: US 1996-716249 19960913 (8)
WO 1995-FR292 19950313 19960913 PCT 371 date
PRIORITY: FR 1994-2950 19940314
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention is directed toward methods and kits for the detection of antibodies associated with autoimmune disorders or infectious agents in an individual employing immunoretroid peptides derived from antigens associated with said disorders and agents. These immunoretroid compounds are derived from the following group of peptides: the foot-and-mouth disease virus major antigenic determinant VP1 peptide [A], the foot-and-mouth disease virus major antigenic determinant VP1 peptide [USA], the influenza virus strain X31 site A peptide, the C-terminal epitope of the histone protein H3 consisting of amino acids 130-135, an internal epitope of the histone protein H3 consisting of amino acids 28-45, an internal epitope of the recombinant 52 kDa autoimmune protein SSA/Ro (Ro52) consisting of amino acids 277-291, an internal epitope of the recombinant 60 kDa autoimmune protein SSA/Ro (Ro60) consisting of amino acids 304-324, the foot-and-mouth disease virus immunodominant loop peptide FP, the foot-and-mouth disease virus immunodominant loop peptide FL, and the foot-and-mouth disease virus immunodominant loop peptide SL. The immunoretroids derived from these peptides are capable of binding to the aforementioned antibodies with equal affinity as compared to the native antigen.

CLM What is claimed is:
1. An in vitro method for the detection of antibodies in an individual comprising the following step: a) contacting a biological sample from an individual suspected of having an autoimmune disorder or infectious agent with an immunoretroid compound under conditions which facilitate the formation of antibody-immunoretroid complexes, wherein said immunoretroid is derived from a protein selected from the group consisting of: the foot-and-mouth disease virus major antigenic determinant VP1 peptide (A), the foot-and-mouth disease virus major antigenic determinant VP1 peptide (USA), the influenza virus strain X31 site A peptide, the C-terminal epitope of the histone protein H3 consisting of amino acids 130-135, an internal epitope of the histone protein H3 consisting of amino acids 28-45, an internal epitope of the recombinant 52 kDa autoimmune protein SSA/Ro (Ro52) consisting of amino acids 277-291, an internal epitope of the recombinant 60 kDa autoimmune protein SSA/Ro (Ro60) consisting of amino acids 304-324, the foot-and-mouth disease virus immunodominant loop peptide FP, the foot-and-mouth disease virus immunodominant loop peptide FL, and the foot-and-mouth disease virus immunodominant loop SL, and wherein said immunoretroid is further capable of binding to protein-specific antibodies with at least an equal affinity as compared to the protein, and b) detecting said antibody-immunoretroid complex formation.

2. The method of claim 1 wherein said immunoretroid is a retro-inverso peptide or a retro-peptide.

3. The method of claim 1, wherein the protein is selected from the group consisting of SEQ ID NO:s 1, 2, 5, 7, 8, 9, 10, 11, 12 and 13.

4. The method of claim 1 wherein said antibodies are produced in said patient by reaction to a first compound selected from the group consisting of a retro-inverso peptide of said protein; a retro-peptide of said protein; said protein; a retro-peptide of an enantiomer of said protein; and an enantiomer of said protein.

5. An immune complex comprising an immunoretroid compound and an antibody specifically bound thereto, wherein said immunoretroid is derived from a protein selected from the group consisting of the foot-and-mouth disease virus major antigenic determinant VP1 peptide (A), the foot-and-mouth disease virus major antigenic determinant VP1 peptide (USA), the influenza virus strain X31 site A peptide, the C-terminal epitope of the histone protein H3 consisting of amino acids 130-135, an internal epitope of the histone protein H3 consisting of amino acids 28-45, an internal epitope of the recombinant 52 kDa autoimmune protein SSA/Ro (Ro52) consisting of amino acids 277-291, an internal epitope of the recombinant 60 kDa autoimmune protein SSA/Ro (Ro60) consisting of amino acids 304-324, the foot-and-mouth disease virus immunodominant loop peptide FP, the foot-and-mouth disease virus immunodominant loop peptide FL, and the foot-and-mouth disease virus immunodominant loop SL.

6. The immune complex of claim 5 wherein said immunoretroid compound is a retro-peptide or retro-inverso peptide.

7. A diagnostic kit for the detection of antibodies associated with an autoimmune disorder or infectious agent in an individual comprising the following components: a first container comprising an immunoretroid compound which is derived from a protein selected from the group consisting of: the foot-and-mouth disease virus major antigenic determinant VP1 peptide (A), the foot-and-mouth disease virus major antigenic determinant VP1 peptide (USA), the influenza virus strain X31 site A peptide, the C-terminal epitope of the histone protein H3 consisting of amino acids 130-135, an internal epitope of the histone protein H3 consisting of amino acids 28-45, an internal epitope of the recombinant 52 kDa autoimmune protein SSA/Ro (Ro52) consisting of amino acids 277-291, an internal epitope of the recombinant 60 kDa autoimmune protein SSA/Ro (Ro60) consisting of amino acids 304-324, the foot-and-mouth disease virus immunodominant loop peptide FP, the foot-and-mouth disease virus immunodominant loop peptide FL, and the foot-and-mouth disease virus immunodominant loop SL, wherein said immunoretroid compound is capable of binding to protein-specific antibodies with at least an equal affinity as compared to the protein; a second container comprising reaction buffers to facilitate the formation of antibody-immunoretroid complexes; and a third container comprising a detection reagent capable of identifying said antibody-immunoretroid complexes.

L4 ANSWER 15 OF 38 MEDLINE on STN
1999121111 Document Number: 99121111. PubMed ID: 9920919. **Solution structure of a retro-inverso peptide analogue mimicking the foot-and-mouth disease virus major antigenic site. Structural basis for its antigenic cross-reactivity with the parent peptide. Petit M C; Benkirane N; Guichard G; Du A P; Marraud M; Cung M T; Briand J P; Muller S. (Laboratoire de Chimie-Physique Macromoleculaire, UMR 7568 CNRS, ENSIC-INPL, 54000 Nancy, France.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Feb 5) 274 (6) 3686-92.** Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The antigenic activity of a 19-mer peptide corresponding to the major antigenic region of foot-and-mouth disease virus and its retro-enantiomeric analogue was found to be completely abolished when they were tested in a biosensor system in trifluoroethanol. This suggests that the folding pattern, which is alpha-helix in trifluoroethanol (confirmed by CD measurement), does not correspond to the biologically relevant conformation(s) recognized by antibodies. The NMR structures of both peptides were thus determined in aqueous solution. These studies showed that the two peptides exhibit similar folding features, particularly in their C termini. This may explain in part the cross-reactive properties of the two peptides in aqueous solution. However, the retro-inverso analogue appears to be more rigid than the parent peptide and contains five atypical beta-turns. This feature may explain why retro-inverso foot-and-mouth disease virus peptides are often better recognized than the parent peptide by anti-virion antibodies.

L4 ANSWER 19 OF 38 MEDLINE on STN
1998024168 Document Number: 98024168. PubMed ID: 9356486. **A retro-inverso peptide corresponding to the GH loop of foot-and-mouth disease virus elicits high levels of long-lasting protective neutralizing antibodies. Briand J P; Benkirane N; Guichard G; Newman J F; Van Regenmortel M H; Brown F; Muller S. (Institut de Biologie Moleculaire et Cellulaire, Unite Propre de Recherche 9021, Centre National de la Recherche Scientifique, Strasbourg, France.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Nov 11) 94 (23) 12545-50.** Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Peptides corresponding to the immunodominant loop located at residues 135-158 on capsid protein VP1 of foot-and-mouth disease virus (FMDV) generally elicit high levels of anti-peptide and virus-neutralizing antibodies. In some instances, however, the level of neutralizing antibodies is low or even negligible, even though the level of anti-peptide antibodies is high. We have shown previously that the antigenic activity of peptide 141-159 of VP1 of a variant of serotype A can be mimicked by a retro-inverso (all-D retro or retroenantio) peptide analogue. This retro-inverso analogue induced greater and longer-lasting antibody titers than did the corresponding L-peptide. We now show that a single inoculation of the retro-inverso analogue elicits high levels of neutralizing antibodies that persist longer than those induced against the corresponding L-peptide and confer substantial protection in guinea pigs challenged with the cognate virus. In view of the high stability to proteases of retro-inverso peptide analogues and their enhanced immunogenicity, these results have practical relevance in designing potential peptide vaccines.

L4 ANSWER 21 OF 38 MEDLINE on STN
97249852 Document Number: 97249852. PubMed ID: 9095678. **Structural**

comparison between retro-inverso and parent peptides: molecular basis for the biological activity of a retro-inverso analogue of the immunodominant fragment of VP1 coat protein from foot-and-mouth disease virus. Carver J A; Esposito G; Viglino P; Fogolari F; Guichard G; Briand J P; Van Regenmortel M H; Brown F; Mascagni P. (Dipartimento di Scienze e Tecnologie Biomediche Universita di Udine, Italy.) BIOPOLYMERS, (1997 Apr 15) 41 (5) 569-90. Journal code: 0372525. ISSN: 0006-3525. Pub. country: United States. Language: English.

AB Antibodies induced against intact foot-and-mouth disease Virus (FMDV) particles bind to the retro-inverso analogue of fragment 141-159 of the viral coat protein VP1 of FMDV, variant A, equally well as to the parent peptide. A conformational investigation of this retro-inverso peptide was carried out by nmr spectroscopy and restrained molecular modeling in order to identify the structural basis for the antigenic mimicry between these retro-inverso and parent peptides. In 100% trifluoroethanol a well-defined left-handed alpha-helical region exists from residue 150 to residue 159, which is consistently present in all conformational families obtained from restrained modelling. A less-defined left-handed helical region is present in the tract 144-148, which is also consistent for all structures. Conformational flexibility exists about Gly149, which leads to two types of structures, either bent or linear. In the bent structures, a three-residue inverse tight turn is found, which can be classified as an inverse gamma-turn centered at Gly149. The overall structural features of the retro-inverso peptide are shown to be similar to those of the parent L-peptide. The two molecules, however, are roughly mirror images because they share inherently chiral secondary structure elements. By comparing these conformational conclusions with the x-ray structure of the Fab complex of a corresponding VP1 antigenic fragment, a rationale is proposed to account for the topological requirements of specific recognition that are implied by the equivalent antigenic activity of the natural and retro-inverso compounds.

L4 ANSWER 30 OF 38 MEDLINE on STN
95400044 Document Number: 95400044. PubMed ID: 7670228. **Enhanced immunogenicity and cross-reactivity of retro-inverso peptidomimetics of the major antigenic site of foot-and-mouth disease virus. Muller S; Guichard G; Benkirane N; Brown F; Van Regenmortel M H; Briand J P. (Institut de Biologie Moleculaire et Cellulaire, UPR 9021 CNRS, Strasbourg, France.) PEPTIDE RESEARCH, (1995 May-Jun) 8 (3) 138-44.** Journal code: 8913494. ISSN: 1040-5704. Pub. country: United States. Language: English.

AB Retro-inverso analogues of peptides corresponding to the major antigenic site 141-159 of VP1 from two foot-and-mouth disease virus variants have been synthesized and tested for their antigenic and immunogenic properties. Antibodies to the L- and retro-inverso peptides were produced by injecting rabbits with peptides covalently coupled to small unilamellar liposomes containing monophosphoryl lipid A as adjuvant. When compared to the antibody response raised against the L-peptides, the duration of the IgG response that was induced by the retro-inverso peptides was significantly longer and the titer of anti-peptide antisera was much higher. Antibodies to retro-inverso peptides cross-reacted equally well with the respective parent L-peptides. These results, obtained with a viral sequence which was found previously to represent a good candidate for possible vaccination, show that retro-inverso peptidomimetics could be useful for enhancing the immunogenicity of peptides.

L8 ANSWER 108 OF 128 MEDLINE on STN
85159117 Document Number: 85159117. PubMed ID: 2580027. **Synthetic**

peptides as antigens: pitfalls of conjugation methods. Briand J P ; Muller S; Van Regenmortel M H. JOURNAL OF IMMUNOLOGICAL METHODS, (1985 Apr 8) 78 (1) 59-69. Journal code: 1305440. ISSN: 0022-1759. Pub. country: Netherlands. Language: English.

AB Peptide-carrier conjugates were prepared using 9 different synthetic peptides, 3 carrier proteins and 4 coupling reagents. Residues of the carrier protein that were modified by different coupling reagents (e.g., glutaraldehyde, carbodiimides, bis-diazotized benzidine) were found to elicit specific antibodies that reacted with unrelated carrier proteins treated with the same coupling agent. To demonstrate the presence of peptide antibodies in an antiserum raised against a peptide-carrier conjugate, it was necessary to use a antigen the peptide coupled to another carrier by means of a different coupling agent. Some of the commonly used conjugation methods were found to lead to conjugates of insufficient stability and sometimes also altered the antigenic properties of the peptide moiety. These difficulties can be overcome by additional control experiments designed to test the quality and the peptide-carrier conjugates.

L8 ANSWER 91 OF 128 MEDLINE on STN
91077103 Document Number: 91077103. PubMed ID: 2257127. **Recent advances in solid-phase peptide synthesis and preparation of antibodies to synthetic peptides. Plaue S; Muller S; Briand J P; Van Regenmortel M H. (Neosystem S.A., Strasbourg, France.) BIOLOGICALS, (1990 Jul) 18 (3) 147-57.** Ref: 129. Journal code: 9004494. ISSN: 1045-1056. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Peptides prepared by the solid-phase peptide synthesis (SPPS) approach are used increasingly in biological research, for instance to elicit anti-peptide antibodies that will recognize the intact, cognate protein. Recent advances in SPPS are reviewed, including the use of new coupling reagents, new methods for evaluating peptide purity and new techniques of automated and multiple peptide synthesis. Methods for enhancing peptide immunogenicity are discussed such as the use of adjuvants and liposomes, and of synthetic branched polypeptides as carriers.

L8 ANSWER 39 OF 128 MEDLINE on STN
1999364771 Document Number: 99364771. PubMed ID: 10438060. **Protection of swine from foot-and-mouth disease with one dose of an all-D retro peptide. Nargi F; Kramer E; Mezencio J; Zamparo J; Whetstone C; Van Regenmortel M H; Briand J P; Muller S; Brown F. (Agricultural Research Service, USDA, Plum Island Animal Disease Center, Greenport, NY 11944, USA.) VACCINE, (1999 Jul 16) 17 (22) 2888-93.** Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Nine pigs were given a single inoculum of 100 microg of the all-D retro peptide corresponding to the immunodominant GH loop encompassing residues 141-159 of capsid protein VP1 of foot-and-mouth disease virus serotype A, sub-type 12. The peptide was conjugated to activated keyhole limpet haemocyanin and oil-adjuvanted before inoculation. The animals were challenged eleven weeks post-vaccination by exposing them to a pig which had been infected with the virus by inoculation. Two naive animals were included in the challenge study as controls. One of the vaccinated animals was completely unprotected and two developed very small lesions. None of the six remaining animals exhibited any clinical signs but two developed antibodies against nonstructural proteins indicating that replication of the virus had occurred. No evidence of replication could be detected in the remaining four animals, either by rise in neutralizing antibody titre or by production of antibodies against non-structural

proteins specific for virus replication.

L4 ANSWER 34 OF 38 MEDLINE on STN
95024041 Document Number: 95024041. PubMed ID: 7937888. **Antigenic mimicry of natural L-peptides with retro-inverso-peptidomimetics. Guichard G; Benkirane N; Zeder-Lutz G; van Regenmortel M H; Briand J P; Muller S. (Institut de Biologie Moleculaire et Cellulaire, Unite Propre de Recherche 9021, Centre National de la Recherche Scientifique, Strasbourg, France.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1994 Oct 11) 91 (21) 9765-9.** Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Three analogues of the model peptide of sequence IRGERA corresponding to the COOH-terminal residues 130-135 of histone H3 were synthesized, and their antigenicity, immunogenicity, and resistance to trypsin were compared to those of the natural L-peptide. The three analogues correspond to the D-enantiomer, containing only D-residues, and two retro-peptides containing NH-CO bonds instead of natural peptide bonds. The chirality of each residue was maintained in the retro-peptide and inverted in the retro-inverso-peptide. Antibodies to the four peptide analogues were produced by injecting BALB/c mice with peptides covalently coupled to small unilamellar liposomes containing monophosphoryl lipid A. Each of the four peptide analogues induced IgG antibodies of various subclasses. The IgG3 antibodies reacted similarly with the four analogues, whereas antibodies of the IgG1, IgG2a, and IgG2b isotypes showed strong conformational preferences for certain peptides. The retro-inverso-peptide IRGERA mimicked the structure and antigenic activity of the natural L-peptide but not of the D- and retro-peptides, whereas the retro-peptide IRGERA mimicked the D-peptide but not the L- and retro-inverso-peptides. The equilibrium affinity constants (Ka) of three monoclonal antibodies generated against the L- and D-peptides with respect to the four peptide analogues were measured in a biosensor system. Large differences in Ka values were observed when each monoclonal antibody was tested with respect to the four peptides. The use of retro-inverso-peptides to replace natural L-peptides is likely to find many applications in immunodiagnosis and as potential synthetic vaccines.

L4 ANSWER 31 OF 38 MEDLINE on STN
95386520 Document Number: 95386520. PubMed ID: 7657648. Retro-inverso peptidomimetics as new immunological probes. Validation and application to the detection of antibodies in rheumatic diseases. Briand J P; Guichard G; Dumortier H; Muller S. (Institut de Biologie Moleculaire et Cellulaire, UPR 9021 CNRS, Strasbourg, France.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Sep 1) 270 (35) 20686-91. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Retro-inverso peptides which contain NH-CO bonds instead of CO-NH peptide bonds are much more resistant to proteolysis than L-peptides. Moreover, they have been shown recently to be able to mimic natural L-peptides with respect to poly- and monoclonal antibodies (Guichard, G., Benkirane, N., Zeder-Lutz, G., Van Regenmortel, M. H. V., Briand, J. P., and Muller, S. (1994b) Proc. Natl. Acad. Sci. U.S.A. 91, 9765-9769). We have further tested the capacity of retro-inverso peptidomimetics to serve as possible targets for antibodies produced by lupus mice and by patients with rheumatic autoimmune diseases. Several retro-inverso peptides corresponding to sequences known to be recognized by autoantibodies were synthesized, namely peptides 28-45 and 130-135 of H3, 277-291 of the Ro/SSA 52-kDa protein, and 304-324 of the Ro/SSA 60-kDa protein, and tested with autoimmune sera by enzyme-linked immunosorbent assay. We have found that retro-inverso peptides are recognized as well as or even better

than natural peptides by antibodies from autoimmune patients and lupus mice. This new approach may lead to important progress in the future development of immunodiagnostic assays, particularly in the case of diseases characterized by inflammatory reactions in the course of which the level of degradative enzymes is increased.

L4 ANSWER 25 OF 38 MEDLINE on STN
96342201 Document Number: 96342201. PubMed ID: 8746115. **Structural limitations to antigenic mimicry achievable with retroinverso (all-D-retro) peptides. Guichard G; Muller S; van Regenmortel M; Briand J P; Mascagni P; Giralt E. TRENDS IN BIOTECHNOLOGY, (1996 Feb) 14 (2) 44-5.** Journal code: 8310903. ISSN: 0167-7799. Pub. country: ENGLAND: United Kingdom. Language: English.

L4 ANSWER 24 OF 38 MEDLINE on STN
97006736 Document Number: 97006736. PubMed ID: 8854029. **Mimicry of viral epitopes with retro-inverso peptides of increased stability. Benkirane N; Guichard G; Briand J P; Muller S; Brown F; Van Regenmortel M H. (Institut de Biologie Moleculaire et Cellulaire, CNRS, Strasbourg, France.) DEVELOPMENTS IN BIOLOGICAL STANDARDIZATION, (1996) 87 283-91.** Journal code: 0427140. ISSN: 0301-5149. Pub. country: Switzerland. Language: English.

AB Two major limitations to the use of peptides as synthetic vaccines are their poor immunogenicity and low antigenic cross-reactivity with the epitopes of virus particles. Recently it has been shown that retro-inverso peptides corresponding to an immunodominant epitope of foot-and-mouth disease virus (FMDV) are able to mimic the structure and antigenic activity of natural L-peptides [1]. A series of L- and retro-inverso peptides of the loop 141-159 of the VP1 protein of FMDV has been synthesized. Antibodies to these peptides were produced by injecting rabbits with peptides covalently coupled to small unilamellar liposomes containing monophosphoryl lipid A as adjuvant. The retro-inverso peptides led to higher serum antibody titres which appeared earlier after the start of immunization and lasted longer than those found with L-peptides. Antibodies to retro-inverso peptides cross-reacted strongly with L-peptides and with virus particles, while guinea pig antisera to VP1 protein and virions cross-reacted strongly with the retro-inverso peptides. In view of their increased stability compared to natural L-peptides, retro-inverso peptidomimetics have considerable potential as synthetic viral vaccines.

L4 ANSWER 23 OF 38 MEDLINE on STN
97125956 Document Number: 97125956. PubMed ID: 8969178. **Exploration of requirements for peptidomimetic immune recognition. Antigenic and immunogenic properties of reduced peptide bond pseudopeptide analogues of a histone hexapeptide. Benkirane N; Guichard G; Briand J P; Muller S. (Institut de Biologie Moleculaire et Cellulaire, UPR 9021 CNRS, 15, rue Descartes, 67000 Strasbourg, France.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Dec 27) 271 (52) 33218-24.** Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB We present a detailed analysis of the antigenic and immunogenic properties of a series of very stable peptidomimetics of a model hexapeptide corresponding to the C-terminal residues 130-135 of histone H3. Five pseudopeptide analogues of the natural sequence IRGERA were synthesized by systematically replacing, in each analogue, one peptide bond at a time by a reduced peptide bond Psi(CH2-NH). Three important features of the resulting analogues were examined. First, the analogues were tested in a biosensor system for their ability to bind monoclonal antibodies generated

against the parent natural peptide, and their kinetic rate constants were measured. The results show that reduced peptide bond analogues can very efficiently mimic the parent peptide. The position of reduced bonds which were deleterious for the binding was found to depend on the antibody tested, and one monoclonal antibody recognized all five analogues. The equilibrium affinity constant toward reduced peptide bond analogues of four antibodies of IgG1 isotype induced against the parent hexapeptide was higher (up to 670 times) with certain analogues than toward the homologous peptide. Second, immunogenic properties of the five analogues were studied, and it was found that polyclonal antibodies induced against analogues in which Psi(CH2-NH) bonds were introduced between residues 130-131, 131-132, and 132-133 (R1-R2, R2-R3, and R3-R4) cross-reacted strongly with the cognate protein H3. Third, we tested the protease resistance of analogues. Altogether, the results provide a strong support for the potent applicability of reduced peptide bond pseudopeptides as components of synthetic vaccines and open a new field for the development of immunomodulatory agents.

L11 ANSWER 5 OF 11 MEDLINE on STN
94075310 Document Number: 94075310. PubMed ID: 8253750. **Antigenicity and immunogenicity of modified synthetic peptides containing D-amino acid residues. Antibodies to a D-enantiomer do recognize the parent L-hexapeptide and reciprocally. Benkirane N; Friede M; Guichard G; Briand J P; Van Regenmortel M H; Muller S. (Institut de Biologie Moleculaire et Cellulaire, UPR 9021 Centre National de la Recherche Scientifique, Strasbourg, France.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1993 Dec 15) 268 (35) 26279-85.** Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The effect of introducing D-amino acid residues in an hexapeptide was examined both at the antigenic and immunogenic levels. A series of D-analogues of the model peptide of sequence IRGERA corresponding to the COOH-terminal residues 130-135 of histone H3 were produced. Four analogues contained a single change of an L-residue by the corresponding enantiomer, one peptide contained two D-residues and another one contained only D-residues (D-enantiomer). A peptide analogue was also synthesized in which the 2 Arg residues were replaced by Lys residues. The parent peptide and peptide analogues were injected into mice after covalent coupling to small unilamellar liposomes containing monophosphoryl lipid A as adjuvant. The substitution of L-Arg131 to Lys or D-Arg was found to change neither the antigenic nor immunogenic properties of the resulting peptides. In contrast, **the substitution of Glu133, Arg134, and Ala135 by the respective enantiomers drastically altered the antigenicity of the modified peptides.** Each of the six D-analogues induced an immune response with an unusually high level of IgG3 antibodies. The D-enantiomer produced IgG3 antibodies which reacted with the homologous peptide as well as with the all L-peptide and the parent protein H3 in solution but not with analogues containing one or two D-residues only. IgG3 antibodies produced against the all L-peptide reacted with the free all D-peptide but not with the other analogues containing D-residues in position 133, 134, and 135.

L12 ANSWER 2 OF 3 MEDLINE on STN
95024041 Document Number: 95024041. PubMed ID: 7937888. **Antigenic mimicry of natural L-peptides with retro-inverso-peptidomimetics. Guichard G; Benkirane N; Zeder-Lutz G; van Regenmortel M H; Briand J P; Muller S. (Institut de Biologie Moleculaire et Cellulaire, Unite Propre de Recherche 9021, Centre National de la Recherche Scientifique, Strasbourg, France.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1994 Oct 11) 91 (21) 9765-9.** Journal code: 7505876.

ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Three analogues of the model peptide of sequence IRGERA corresponding to the COOH-terminal residues 130-135 of histone H3 were synthesized, and their antigenicity, immunogenicity, and resistance to trypsin were compared to those of the natural L-peptide. The three analogues correspond to the D-enantiomer, containing only D-residues, and two retro-peptides containing NH-CO bonds instead of natural peptide bonds. The chirality of each residue was maintained in the retro-peptide and inverted in the retro-inverso-peptide. Antibodies to the four peptide analogues were produced by injecting BALB/c mice with peptides covalently coupled to small unilamellar liposomes containing monophosphoryl lipid A. Each of the four peptide analogues induced IgG antibodies of various subclasses. The IgG3 antibodies reacted similarly with the four analogues, whereas antibodies of the IgG1, IgG2a, and IgG2b isotypes showed strong conformational preferences for certain peptides. The retro-inverso-peptide IRGERA mimicked the structure and antigenic activity of the natural L-peptide but not of the D- and retro-peptides, whereas the retro-peptide IRGERA mimicked the D-peptide but not the L- and retro-inverso-peptides. The equilibrium affinity constants (Ka) of three monoclonal antibodies generated against the L- and D-peptides with respect to the four peptide analogues were measured in a biosensor system. Large differences in Ka values were observed when each monoclonal antibody was tested with respect to the four peptides. The use of retro-inverso-peptides to replace natural L-peptides is likely to find many applications in immunodiagnosis and as potential synthetic vaccines.

L12 ANSWER 3 OF 3 MEDLINE on STN
94075310 Document Number: 94075310. PubMed ID: 8253750.
Antigenicity and immunogenicity of modified synthetic peptides containing D-amino acid residues. Antibodies to a D-enantiomer do recognize the parent L-hexapeptide and reciprocally. Benkirane N ; Friede M; Guichard G; Briand J P; Van Regenmortel M H; Muller S. (Institut de Biologie Moleculaire et Cellulaire, UPR 9021 Centre National de la Recherche Scientifique, Strasbourg, France.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1993 Dec 15) 268 (35) 26279-85. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The effect of introducing D-amino acid residues in an hexapeptide was examined both at the antigenic and immunogenic levels. A series of D-analogues of the model peptide of sequence IRGERA corresponding to the COOH-terminal residues 130-135 of histone H3 were produced. Four analogues contained a single change of an L-residue by the corresponding enantiomer, one peptide contained two D-residues and another one contained only D-residues (D-enantiomer). A peptide analogue was also synthesized in which the 2 Arg residues were replaced by Lys residues. The parent peptide and peptide analogues were injected into mice after covalent coupling to small unilamellar liposomes containing monophosphoryl lipid A as adjuvant. The substitution of L-Arg131 to Lys or D-Arg was found to change neither the antigenic nor immunogenic properties of the resulting peptides. In contrast, the substitution of Glu133, Arg134, and Ala135 by the respective enantiomers drastically altered the antigenicity of the modified peptides. Each of the six D-analogues induced an immune response with an unusually high level of IgG3 antibodies. The D-enantiomer produced IgG3 antibodies which reacted with the homologous peptide as well as with the all L-peptide and the parent protein H3 in solution but not with analogues containing one or two D-residues only. IgG3 antibodies produced against the all L-peptide reacted with the free all D-peptide but not with the other analogues containing D-residues in position 133, 134, and 135.

L15 ANSWER 2 OF 2 MEDLINE on STN
85156667 Document Number: 85156667. PubMed ID: 6099336. **Solid phase synthesis of retro-inverso peptide analogues. Synthesis and biological activity of the partially modified retro-inverso analogue of the bradykinin potentiating peptide BPP9a [gLys6, (RS)-mPhe7, Ala8] BPP9a. Bonelli F; Pessi A; Verdini A S. INTERNATIONAL JOURNAL OF PEPTIDE AND PROTEIN RESEARCH, (1984 Dec) 24 (6) 553-6.** Journal code: 0330420. ISSN: 0367-8377. Pub. country: Denmark. Language: English.

AB The solid phase synthesis of a partially modified retro-inverso analogue of the bradykinin potentiating peptide BPP9a, [gLys6, (R,S)-mPhe7, Ala8] BPP9a is described. The analogue, which is active in vitro and in vivo, displays prolonged resistance towards cleavage by angiotensin converting enzyme (ACE).

L17 ANSWER 3 OF 3 MEDLINE on STN
96030282 Document Number: 96030282. PubMed ID: 7546569. **Recent developments in retro peptides and proteins--an ongoing topochemical exploration. Chorev M; Goodman M. (Department of Pharmaceutical Chemistry, Faculty of Medicine, Hebrew University, Jerusalem, Israel.) TRENDS IN BIOTECHNOLOGY, (1995 Oct) 13 (10) 438-45.** Ref: 42. Journal code: 8310903. ISSN: 0167-7799. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Main-chain peptidomimetics based on peptide-bond reversal and inversion of chirality represent important structural alterations for peptides and proteins, and are highly significant for biotechnology; these modifications have been widely applied: the D-HIV-protease dimer cleaves only all-D substrate; an all-D-hexapeptide opioid is able to produce analgesia following intraperitoneal administration. Antigenicity and immunogenicity can be achieved by metabolically stable antigens such as all-D- and retro-inverso-isomers of natural antigenic peptides. Isomers, including the retro- and retro-inverso- forms, of hybrid peptides derived from cercropin A and melittin, maintain antimicrobial activity. Therefore, an insight is provided into structure-activity relationships and the rational design of biologically important isomeric peptides.

L18 ANSWER 7 OF 12 MEDLINE on STN
84000795 Document Number: 84000795. PubMed ID: 6616013. Computer simulation of the conformational properties of retro-inverso peptides. II. Ab initio study, spatial electron distribution, and population analysis of N-formylglycine methylamide, N-formyl N'-acetyldiaminomethane, and N-methylmalonamide. Stern P S; Chorev M; Goodman M; Hagler A T. BIOPOLYMERS, (1983 Aug) 22 (8) 1901-7. Journal code: 0372525. ISSN: 0006-3525. Pub. country: United States. Language: English.

L18 ANSWER 8 OF 12 MEDLINE on STN
84000794 Document Number: 84000794. PubMed ID: 6616012. Computer simulation of the conformational properties of retro-inverso peptides. I. Empirical force field calculations of rigid and flexible geometries of N-acetylglycine-N'-methylamide, bis(acetamido) methane, and N,N'-dimethylmalonamide and their corresponding C alpha-methylated analogs. Stern P S; Chorev M; Goodman M; Hagler A T. BIOPOLYMERS, (1983 Aug) 22 (8) 1885-900. Journal code: 0372525. ISSN: 0006-3525. Pub. country: United States. Language: English.

L18 ANSWER 11 OF 12 MEDLINE on STN
83138657 Document Number: 83138657. PubMed ID: 6186812. Synthesis of

partially modified retro-inverso substance P analogues and their biological activity. Chorev M; Rubini E; Gilon C; Wormser U; Selinger Z. JOURNAL OF MEDICINAL CHEMISTRY, (1983 Feb) 26 (2) 129-35. Journal code: 9716531. ISSN: 0022-2623. Pub. country: United States. Language: English.

AB Partial retro-inverso modification of a single peptide bond was applied to pGlu-Phe-Phe-Gly-Leu-Met-NH2 (I), a C-terminal hexapeptide analogue of the neuropeptide substance P. Two analogues with reversed peptide bonds, between the pGlu-Phe and Phe-Gly residues, were prepared, purified and characterized. The analogue gpGlu-(RS)-mPhe-Phe-Gly-Leu-Met-NH2 (II) was devoid of either agonistic or antagonistic activity. The second pseudopeptide analogue, i.e., pGlu-Phe-gPhe-mGly-Leu-Met-NH2 (III), was found to be a full agonist with 22% of the potency of I in the guinea pig ileum assay.

L21 ANSWER 55 OF 115 MEDLINE on STN
96107193 Document Number: 96107193. PubMed ID: 8530469. **Topological mimicry of cross-reacting enantiomeric peptide antigens. Verdoliva A; Ruvo M; Cassani G; Fassina G. (Protein Engineering, Tecnogen S.C.p.A., Parco Scientifico, Piana di Monte Verna (CE), Italy.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Dec 22) 270 (51) 30422-7.** Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Rabbit polyclonal antibodies against multimeric peptide antigens were found to cross-react to a significant extent with topologically related variants of the parent antigen, where the chirality of each amino acid residue (inverso derivatives), or the peptide sequence orientation (retro derivatives), was inverted or where both modifications were simultaneously introduced (retro-inverso derivatives). All peptide variants displayed similar recognition properties for antibodies and similar dose-dependent inhibitory effects on the interaction between immobilized parent antigen and corresponding antibodies. Importance of peptide side chain topology on antigenicity was evaluated analyzing the recognition properties of two sequence-simplified parent peptide variants, one lacking of the side chains in the sequence odd position and the other in even position. These two variants, prepared introducing glycine residues alternatively in the parent peptide sequence, were found to cross-react to a significant extent with the original antibody raised against the parent peptide. Analysis of molecular models of peptide enantiomeric variants in the elongated all-trans configuration suggested that the topological equivalence of alternating side chains could lead to the formation of similar recognition surfaces, thus mimicking the parent peptide antigenic structure.

L21 ANSWER 47 OF 115 MEDLINE on STN
97332614 Document Number: 97332614. PubMed ID: 9188848. **On the immunogenic properties of retro-inverso peptides. Total retro-inversion of T-cell epitopes causes a loss of binding to MHC II molecules. Herve M; Maillere B; Mourier G; Texier C; Leroy S; Menez A. (CEA, Departement d'Ingenierie et d'Etudes des Proteines, CE Saclay, Gif-sur-Yvette, France.) MOLECULAR IMMUNOLOGY, (1997 Feb) 34 (2) 157-63.** Journal code: 7905289. ISSN: 0161-5890. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Retro-inversion is considered an attractive approach for drug and vaccine design since it provides the modified peptides with higher resistance to proteolytic degradation. We therefore investigated in detail the effect of retro-inversion on the immunological properties of synthetic peptides. We have synthesized retro-inverso analogues of MHC II

restricted peptides that thus contained the correct orientation of the side chains but an inverse main chain. Retro-inversion made the peptides unable to compete in I E(d) or I A(d) binding tests, demonstrating a very low, if any, capacity to bind to MHC II molecules. These results confirm previous structural data that hydrogen bonds between residues of MHC II molecules and the main chain of antigenic peptides play a major interacting role. In vito experiments further showed that retro-inversion of a T-cell epitope causes its inability to either sustain in vitro T-cell stimulation or to prime specific T cells. Moreover, **the retro-inverso peptide was not recognized by antibodies raised against the native peptide and did not elicit antibodies when injected into BALB/c mice. Retro-inverso peptides appear to be poor immunogens as a result of their weak capacity to bind to MHC II molecules.** As an advantage, they are not expected to trigger undesirable humoral responses such as hypersensitivity or allergic disease. These results also provide a molecular explanation regarding the weak immunogenicity of D-amino acids containing polypeptides.

L21 ANSWER 41 OF 115 MEDLINE on STN
1998386733 Document Number: 98386733. PubMed ID: 9720264. **D-peptides as immunogens and diagnostic reagents. Van Regenmortel M H; Muller S. (UPR 9021, IBMC, CNRS, Strasbourg, France.) CURRENT OPINION IN BIOTECHNOLOGY, (1998 Aug) 9 (4) 377-82.** Ref: 37. Journal code: 9100492. ISSN: 0958-1669. Pub. country: ENGLAND: United Kingdom. Language: English.

AB There has been a regain of interest in the immunological applications of peptides assembled partly or totally from D-amino acids. Such peptides are much more stable to proteolysis than natural L-peptides and they have considerable potential as synthetic vaccines and as immunomodulators in T-cell responses. Retro-inverso, also called retro-all-D or retroenantio, peptide analogues that closely mimic the structure of protein antigens are obtained by assembling amino acid residues in the reverse order from that in the parent peptides and replacing L- by D-amino acids. Retro-all-D peptides corresponding to an immunodominant epitope of foot-and-mouth disease virus have been shown to elicit high levels of neutralizing antibodies in experimental animals. Certain retro-all-D peptide analogues of T-cell epitopes are able to bind to MHC class II molecules and may either lead to T-cell activation or inhibit deleterious T-cell responses.

L21 ANSWER 6 OF 115 MEDLINE on STN
2003031375 Document Number: 22426486. PubMed ID: 12538696. **Mimicry of native peptide antigens by the corresponding retro-inverso analogs is dependent on their intrinsic structure and interaction propensities. Nair Deepak T; Kaur Kanwal J; Singh Kavita; Mukherjee Paushali; Rajagopal Deepa; George Anna; Bal Vineeta; Rath Satyajit; Rao Kanury V S; Salunke Dinakar M. (National Institute of Immunology, New Delhi, India.) JOURNAL OF IMMUNOLOGY, (2003 Feb 1) 170 (3) 1362-73.** Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Retro-inverso (ri) analogs of model T cell and B cell epitopes were predictively designed as mimics and then assayed for activity to understand the basis of functional ri-antigenic peptide mimicry. ri versions of two MHC class I binding peptide epitopes, one from a vesicular stomatitis virus glycoprotein (VSV(p)) and another from OVA (OVAp), exhibit structural as well as functional mimicry of their native counterparts. The two ri peptides exhibit conformational plasticity and they bind to MHC class I (H-2K(b)) similar to their native counterparts both in silico and in vivo. In fact, ri-OVAp is also presented to an

OVAp-specific T cell line in a mode similar to native OVAp. In contrast, **the ri version of an immunodominant B cell peptide epitope from a hepatitis B virus protein, PS1, exhibits no structural or functional correlation with its native counterpart.** PS1 and its ri analog do not exhibit similar conformational propensities. PS1 is less flexible relative to its ri version. These observed structure-function relationships of the ri-peptide epitopes are consistent with the differences in recognition properties between peptide-MHC vs peptide-Ab binding where, while the recognition of the epitope by MHC is pattern based, the exquisitely specific recognition of Ag by Ab arises from the high complementarity between the Ag and the binding site of the Ab. It is evident that the correlation of conformational and interaction propensities of native L-peptides and their ri counterparts depends both on their inherent structural properties and on their mode of recognition.

L11 ANSWER 5 OF 11 MEDLINE on STN

94075310 Document Number: 94075310. PubMed ID: 8253750. Antigenicity and immunogenicity of modified synthetic peptides containing D-amino acid residues. Antibodies to a D-enantiomer do recognize the parent L-hexapeptide and reciprocally. Benkirane N; Friede M; Guichard G; Briand J P; Van Regenmortel M H; Muller S. (Institut de Biologie Moleculaire et Cellulaire, UPR 9021 Centre National de la Recherche Scientifique, Strasbourg, France.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1993 Dec 15) 268 (35) 26279-85. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The effect of introducing D-amino acid residues in an hexapeptide was examined both at the antigenic and immunogenic levels. A series of D-analogues of the model peptide of sequence IRGERA corresponding to the COOH-terminal residues 130-135 of histone H3 were produced. Four analogues contained a single change of an L-residue by the corresponding enantiomer, one peptide contained two D-residues and another one contained only D-residues (D-enantiomer). A peptide analogue was also synthesized in which the 2 Arg residues were replaced by Lys residues. The parent peptide and peptide analogues were injected into mice after covalent coupling to small unilamellar liposomes containing monophosphoryl lipid A as adjuvant. The substitution of L-Arg131 to Lys or D-Arg was found to change neither the antigenic nor immunogenic properties of the resulting peptides. In contrast, **the substitution of Glu133, Arg134, and Ala135 by the respective enantiomers drastically altered the antigenicity of the modified peptides**. Each of the six D-analogues induced an immune response with an unusually high level of IgG3 antibodies. The D-enantiomer produced IgG3 antibodies which reacted with the homologous peptide as well as with the all L-peptide and the parent protein H3 in solution but not with analogues containing one or two D-residues only. IgG3 antibodies produced against the all L-peptide reacted with the free all D-peptide but not with the other analogues containing D-residues in position 133, 134, and 135.

L21 ANSWER 47 OF 115 MEDLINE on STN
97332614 Document Number: 97332614. PubMed ID: 9188848. On the immunogenic properties of retro-inverso peptides.
Total retro-inversion of T-cell epitopes causes a loss of binding to MHC II molecules. Herve M; Maillere B; Mourier G; Texier C; Leroy S; Menez A. (CEA, Departement d'Ingenierie et d'Etudes des Proteines, CE Saclay, Gif-sur-Yvette, France.) MOLECULAR IMMUNOLOGY, (1997 Feb) 34 (2) 157-63. Journal code: 7905289. ISSN: 0161-5890. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Retro-inversion is considered an attractive approach for drug and vaccine design since it provides the modified peptides with higher resistance to proteolytic degradation. We therefore investigated in detail the effect of retro-inversion on the immunological properties of synthetic peptides. We have synthesized retro-inverso analogues of MHC II restricted peptides that thus contained the correct orientation of the side chains but an inverse main chain. Retro-inversion made the peptides unable to compete in I E(d) or I A(d) binding tests, demonstrating a very low, if any, capacity to bind to MHC II molecules. These results confirm previous structural data that hydrogen bonds between residues of MHC II molecules and the main chain of antigenic peptides play a major interacting role. In vito experiments further showed that retro-inversion of a T-cell epitope causes its inability to either sustain in vitro T-cell stimulation or to prime specific T cells. Moreover, **the retro-inverso peptide was not recognized by antibodies raised against the native peptide and did not elicit antibodies when injected into BALB/c mice. Retro-inverso peptides appear to be poor immunogens as a result of their weak capacity to bind to MHC II molecules.** As an advantage, they are not expected to trigger undesirable humoral responses such as hypersensitivity or allergic disease. These results also provide a molecular explanation regarding the weak immunogenicity of D-amino acids containing polypeptides.